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EDITORIAL COMMENT

The Elusive Scourge of Sudden Cardiac Death

Is Rational Decision Making Possible? Should There Be Standards of Risks and Predictions in Medicine?*

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Among the many intriguing aspects of heart failure (HF), arguably none is more elusive than predicting sudden cardiac death (SCD). Despite availability of validated risk scores for all-cause mortality prediction for these patients (e.g., the Heart Failure Survival Score and the Seattle Heart Failure Model), there are no such guidelines for predicting SCD (1,2). Multiple electrocardiographic patterns have been correlated with risk of SCD; however, none seem sensitive and specific enough to guide therapy solely on the basis of their results. Initial trials assessing therapy for SCD have used very specific enrollment criteria (i.e., history of SCD survival [with very low sensitivity and as secondary prevention therapy]) or cumbersome criteria such as a need for inducing ventricular tachycardia during electrophysiology study (3). Despite the vigor of this latter approach, electrophysiological study-guided therapy was not adopted widely for primary prevention purposes because the follow-up of patients who were not inducible for arrhythmia (and therefore inaccurately thought to be safe) showed the same risk of death as those patients who refused to participate in the trial and were followed up in a registry.

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Based on these experiences, the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) study enrolled patients with ischemic cardiomyopathy and an ejection fraction of ≤30% and randomly assigned them to receive a defibrillator or standard care (4). The rationale for this approach was sound; these patients are at high risk for SCD that cannot be predicted accurately. This trial was positive for a 9% absolute reduction in all-cause mortality at 3 years. This was followed by the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study, which showed a 7.5% reduction in all-cause mortality at 5 years with a defibrillator (5). This trial included both ischemic and nonischemic patients with an ejection fraction of <36%. The results of these 2 studies swung medical practice from using defibrillators according to least sensitive secondary prevention criteria (i.e., survivors of SCD) to least specific primary prevention criteria: a defibrillator for all with a low ejection fraction.

Which end of the spectrum is appropriate is a matter of debate. Clearly waiting for syncope or SCD as an eligibility criterion is too restrictive, because patients may not survive the initial arrhythmic episode. But should everyone with heart failure and moderate systolic dysfunction get a defibrillator? Proponents would argue that liberal indications give patients the best result. One should be careful in phrasing this assertion; a defibrillator for all gives the patients *on average* the best result. Opponents would argue that the costs to society are not justifiable, because many patients will not benefit from a defibrillator. They will either never have ventricular arrhythmias, or if they do, not all defibrillator shocks will be able to sustain life for these failing ventricles, or the defibrillators will do nothing to address comorbid conditions leading to death. Thus, at both ends of the disease spectrum, the benefit may be marginal. In addition to the costs and futility are issues related to procedure complications, and more importantly, the unanswered questions regarding quality of life with defibrillators in regard to end-of-life issues.

The search for high-risk category patients who are likely to benefit the most from a defibrillator has been slow for multiple reasons. Predicting SCD can be difficult. There exists a disincentive for physicians, hospitals, and industry to narrow the indications. This is partly because of the monetary incentive, but also because of the fear of malpractice risk if a patient with heart failure dies suddenly without a defibrillator. The combination of financial incentives and fear of litigation have a pervasive effect across medical practice.

In an environment of everything for all, the study by Goldenberg et al. (6) in this issue of the *Journal* provides further evidence that a defibrillator does not help all heart failure patients. In this secondary analysis of the MADIT-II database, the investigators show that patients with preserved systolic blood pressure benefit little, if at all, from a defibrillator. Whether this represents a special pathophysiological relationship between blood pressure and risk of SCD, or simply that preserved blood pressure is a marker of healthier patient overall, can be debated. These results obviously must be taken with caution. This is only one study, this was a secondary analysis with limited power on data not collected specifically to answer this question, and the patient population was restricted to the enrollment criteria of MADIT-II study. Therefore, the results need to be validated by other studies in a wider patient population.

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However, this study reinforces the need for research to improve rational medical decision making.

Ideally the initial study designs for MADIT-II and SCD-HeFT should have randomly assigned patients stratified by ejection fraction ranges or other important heart failure risk predictors. Moreover the impact of comorbidities should have been taken into account up front. However, the increase in the number of patients needed to achieve statistical power with this approach would have increased the cost to the study sponsor. The easiest and cheapest way was to cast wider nets. However, we may have answered some very important questions prospectively, instead being left to tease answers to important clinical questions by retrospective and less-than-optimal analyses.

Let us return to the original problem: why do we have prediction models for all-cause mortality but not for SCD? Is the prediction of SCD so different from all-cause mortality? The answer may have more to do with our risk tolerance than risk assessment per se. The c-statistics for all-cause mortality (a measure to describe the variability in outcome explained by the prediction rule) in the derivation data sets for the Heart Failure Survival Score and the Seattle Heart Failure Model were 0.74 and 0.72, respectively. In other words, more than one-quarter of the outcome variability could not be explained by either model. Yet these models are accepted and used in medical practice routinely (e.g., in transplant listings). Why is it that this degree of uncertainty is acceptable by the medical community for all-cause mortality prediction? It may be because from an all-cause mortality perspective, beyond transplantation there is nothing to offer to these patients barring left ventricular assist devices, which is a field under investigation. Because of the severe donor organ shortage, even if a patient with a "better" predicted outcome dies, it does not matter as much because we are currently not able to save all of the "sicker" ones anyway. Also, many of these patients will have a worsening clinical course over time and one can adjust their scores and hence prediction of all-cause mortality.

Can we develop similar risk scores for SCD based on multiple patient characteristics and comorbidities that perform as well? If not for SCD per se, then at least for predicting whether a patient will benefit from a defibrillator? Of course we can, and some investigators have attempted to do so (7). However, whether will they be accepted by the medical profession is not certain. A c-statistic of 0.75 or even 0.80 probably will not be good enough to change practice for an off-the-shelf technology such as a defibrillator, primarily because the degree of uncertainty and the level of acceptable risk have not been defined.

Should there be a standard of "low risk" when we should not place defibrillators? For better or for worse, the medical community has accepted the notion of cost effectiveness. Renal replacement therapy with dialysis is an accepted benchmark. Any new therapy must stand the test of being in the ballpark of dialysis with respect to cost effectiveness before it is widely accepted by the medical community. Should the medical community also develop some standards for the predictive capabilities for tests and scores? Should there be acceptable risk thresholds?

Prediction of the future is an inherent daily part of medical practice; however, no standards for an acceptable sensitivity and specificity of tests or predictive capabilities of prediction rules are discussed. The details of doing this will be complicated, but perhaps the time has come that it must be done. This is not only applicable for defibrillators but also for many new diagnostic and therapeutic technologies. And one may argue that once we can define as a society what level and accuracy of prediction is acceptable to us and what risk is tolerable, and in turn we are legally protected by making those decisions, only then will we be able to practice more rational medicine. If a test or a formula based on multiple patient characteristics puts a patient at <10% risk of SCD, should we not implant a defibrillator? Or should the threshold be 5%? The question is not whether we can or cannot predict risk, the question is what risk are we ready to tolerate? Until we answer these difficult questions, "everything for all" medicine is likely to continue. The stakes are too high otherwise. But we must accept that this approach is unsustainable, and if the medical community does not take the lead to answer these important questions, government, regulators, payers, or someone else will!

Defibrillators do not stop the inevitable; they delay death, not prevent it. Delaying death may not always be for the best. Not everyone with a defibrillator uses it, and not everyone who uses it benefits from it. Patients with a defibrillator also die, as does everyone! In this light, the article by Goldenberg et al. (6) in this issue of the *Journal*, although limited in scope, is a welcome addition to this growing field, and the authors should be commended for their effort.

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